TREATMENT OF GRAM-NEGATIVE BACTEREMIA AND SHOCK WITH HUMAN ANTISERUM TO A MUTANT *ESCHERICHIA COLI*

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Abstract In an effort to decrease deaths from gram-negative bacteremia and endotoxin shock, we treated bacteremic patients with human antiserum to endotoxin (lipopolysaccharide) core. Antiserum was prepared by vaccinating healthy men with heat-killed *Escherichia coli* J5; this mutant lacks lipopolysaccharide oligosaccharide side chains, so that the core, which is nearly identical to that of most other gram-negative bacteria, is exposed for antibody formation. In a randomized controlled trial, patients were given either J5 antiserum or preimmune control serum intravenously, near the onset of illness. The number of deaths in the bacteremic patients was 42 of 109 (39 per cent) in controls and 23 of 103 (22 per cent) in recipients of J5 antiserum ($P = 0.011$). In those with profound shock, mortality was 30 of 39 (77 per cent) in controls and 18 of 41 (44 per cent) in recipients of J5 antiserum ($P = 0.003$). We conclude that human antiserum to the lipopolysaccharide core can substantially reduce deaths from gram-negative bacteremia. (N Engl J Med. 1982; 307:1225-30.)

DEATHS from gram-negative bacteremia continue to occur at a high frequency despite the advent of potent antibiotics and aggressive support techniques.[1,2] Antibiotic resistance and the severity of underlying disease account in part for the failure of conventional treatment,[2,3] but there are several reasons for postulating that the lipopolysaccharide, or endotoxin, in the cell wall of invading bacteria is an important factor in mortality. First of all, endotoxin on the surface of circulating bacteria is in a position to activate biologic mediators of shock even if the amount of free, solubilized endotoxin is below detectable levels. Secondly, the clinical features of gram-negative bacteremia — fever, shock, disseminated intravascular coagulation, complement activation, and transient leukopenia followed by leukocytosis — are identical to the effects of intravenously administered endotoxin.[4-6] Thirdly, antibiotics cannot be expected to reverse these phenomena; in some cases they have been thought to aggravate them briefly when bacteria have been killed.[7,8] For these reasons we thought that an antibody that could neutralize the endotoxin might improve survival in gram-negative bacteremia.

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Supported by a grant (AI 10108) from the U.S. Public Health Service and by a U.S. Army contract (MED/DADA 17-69-C-9161).

Presented in part at the 94th annual meeting of the Association of American Physicians, San Francisco, April 25, 1981.

Our approach to the development of a protective antiserum was based on the following structural and immunogenic properties of bacterial lipopolysaccharides. In general, they are composed of three portions: the oligosaccharide side chains, the core polysaccharide, and lipid A, which is considered to be the toxic moiety. Antibody to complete lipopolysaccharide is directed primarily against the side chains, which differ widely from strain to strain. Such antiserum protects against the biologic effects of lipopolysaccharide from the immunizing bacterial strain but is much less effective against lipopolysaccharide from other strains. There is much less strain variation in the core polysaccharide–lipid A complex than in the side chains. In fact, the core regions of most gram-negative bacteria contain very similar lipopolysaccharide-core structures.[9,10] We therefore reasoned that the antigenic diversity of clinically important but unrelated gram-negative bacteria might be circumvented if we used as a vaccine a strain of bacteria defective in side chains and containing only core elements in its lipopolysaccharide. The strain that we chose was the J5 mutant of *Escherichia coli* 0111:B_4, a mutant lacking both the enzyme uridine 5′-diphosphate-galactose 4-epimerase and the ability to incorporate exogenous galactose into its lipopolysaccharide. The epimerase deficiency prevents attachment of side chains to core polysaccharide,[11] and the defect in galactose incorporation, still to be characterized, confers phenotypic stability. Thus, lipopolysaccharide from the J5 mutant consists solely of core determinants: lipid A, *N*-acetylglucosamine, 2-keto-3-deoxyoctonate, heptose, and glucose.

We found that rabbits immunized with J5, prepared

Reprinted from the *New England Journal of Medicine*
307:1225-1230 (November 11), 1982